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March 5, 2002

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Daniel Troy, Esq.
Chief Counsel
Office of the Chief Counsel
Food and Drug Administration
5600 Fishes Lane, GCF-1
Rockville, MD 20857

Re: Final Order to Revoke 21 C.F.R. § 310.500

Dear Mr. Troy:

On January 8, 2002, I sent you a letter (copy attached) concerning the fact that the agency has allowed over one year to pass since it published a proposed rule to revoke 21 C.F.R. § 310.500 (65 Fed. Reg. 70538 (Nov. 24, 2000)) which would remove unapproved digoxin products from the market. You were thoughtful in responding to my letter on February 13, which is appreciated. However, we remain concerned that finalizing the regulation is languishing at the agency despite a clear public health risk. Again, we request that your office and the agency devote the necessary resources to finalize this regulation so that the public can be protected.

Very truly yours,

Gary L. Yingling

Enclosure

cc: Dockets Management Branch, Dockets No. 00N-1609 and 00N-1610

00N-1609

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January 8, 2002

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Dear Mr. Troy:

We submit this letter in an effort to follow up on an issue that, in our opinion, has languished at the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER), despite the public health risk and broad industry compliance implications. This issue is the continued marketing of unapproved digoxin tablets and CDER's lack of action to remove these products from the marketplace.

You may recall that, on October 4, 2000, Bertek Pharmaceuticals Inc. (Bertek) and Amide Pharmaceutical, Inc. (Amide) filed a complaint against FDA in Federal District Court. *Bertek Pharmaceuticals Inc. v. Henney*, Civ. Action No. 1:00CV02393 (D.D.C., Oct. 4, 2000). In the lawsuit, Bertek and Amide alleged that FDA, by its inaction, was authorizing and condoning the illegal marketing of unapproved digoxin tablets because the agency permitted the continued marketing of these products without an approved new drug application (NDA), in conflict with its statutory mandate to require prior approval for all new drugs. The parties settled the suit by way of a Declaratory Judgment, signed by the court on November 21, 2000. In that Declaratory Judgment, FDA provided a commitment that it would initiate a rulemaking proceeding to revoke the digoxin batch certification provision published at 21 C.F.R. § 310.500. Subsequently, FDA issued a notice in the *Federal Register* reaffirming that digoxin products for oral use are new drugs and requiring the submission of new drug applications for continued marketing. 65 Fed. Reg. 70573 (Nov. 24, 2000). FDA also published a Proposed Rule to revoke 21 C.F.R. § 310.500. 65 Fed. Reg. 70538 (Nov. 24, 2000). Over one year later, FDA has failed to take any further action with respect to digoxin products. As a result, there is no incentive for the manufacturers of unapproved digoxin products to comply with the NDA requirements.

We urge FDA to promptly issue a Final Rule on this matter and remove any unapproved digoxin tablets from the market. FDA already has determined that a public health risk exists because unapproved digoxin tablets with unsubstantiated bioequivalence and disparate labeling claims remain on the market and may be confused with FDA-approved digoxin tablets. Only by swiftly removing these unapproved drugs from the market can FDA adequately protect the public health. The agency has all the legal and scientific evidence it needs to pursue additional market

withdrawal proceedings against Jerome Stevens Pharmaceuticals, Inc. and any other manufacturer of "batch-certified" digoxin tablets.

Time is of the essence with respect to publishing a Final Rule in this matter. Under FDA policy, the agency likely will provide digoxin tablet marketers with a reasonable time period to remove their products from the market. As a result, even if the Final Rule is issued tomorrow, unapproved digoxin tablets will remain on the market for a substantial period of time. Consequently, the public health risk that exists today will remain for the foreseeable future until FDA takes further action against the products. Although FDA has proposed that the Final Rule would become effective within 30 days after its issuance (*see* 65 Fed. Reg. 70573), several digoxin makers already have petitioned the agency to delay the effective date and permit the continued marketing of unapproved drugs for another two years. *See* Docket Nos. 00N-1609, 00N-1610; December 22, 2000 Comments from Jerome Stevens Pharmaceuticals, Inc.; February 16, 2001 Comments from Roxane Laboratories; and February 22, 2001 Comments from GlaxoSmithKline. Hence, swift action by FDA is paramount.

Despite the ample notice provided by the Proposed Rule, these companies claim that they need time – at least 2 years -- to prepare and submit drug applications for digoxin products. Yet, a prudent manufacturer would have begun that process at the time the Proposed Rule was published – already over one year ago. By contrast, FDA has estimated that it would take 480 hours, or 12 weeks, to prepare and submit a new drug application for digoxin tablets. 65 Fed. Reg. 70538. Even if the manufacturers had waited until the comment period ended for the Proposed Rule, which was February 22, 2001, their drug applications could have been filed with FDA 12 weeks later, or by May 30, 2001. The manufacturers' requests for a two-year delay cause us to wonder -- are they unwilling to manufacture a digoxin product that complies with the ANDA process, or unable? In either case, the public health concern remains with respect to the simultaneous marketing of bioequivalent and inequivalent products without adequate substitution warnings to physicians and pharmacists. Any further delay in agency action against unapproved digoxin tablets is unwarranted and risks the public health.[1]

We note also that, with regard to the similarly-situated product, levothyroxine sodium, FDA has implemented a phase-down schedule for the distribution of certain unapproved levothyroxine sodium products, culminating in an absolute date when the distribution of any unapproved drugs must cease. *See* FDA Guidance for Industry, Levothyroxine Sodium Products, Enforcement of August 14, 2001 Compliance Date and Submission of New Applications (July 2001). In that Guidance, FDA determined that it would exercise enforcement discretion against those

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[1] If, for some reason, the agency is reluctant to commence the market withdrawal of digoxin elixir products, we see no reason why the agency could not bifurcate the enforcement of digoxin elixir and digoxin tablet products. FDA may conduct two different enforcement actions with respect to the two dosage forms. In the alternative, FDA could continue to handle both types of products pursuant to the same enforcement notice, but develop a separate schedule that would withdraw the tablets from the market quickly, while providing a longer market withdrawal schedule for the elixir products.

unapproved products for which drug applications were pending, due to concerns about product transition for patients and physicians, as well as production scale-up issues for approved manufacturers. To facilitate public health protection, however, levothyroxine sodium manufacturers would be required to certify that they were reducing the average monthly distribution of unapproved products over a period of months until August 14, 2003 when all distribution must cease. If FDA should find that similar marketing concerns exist for digoxin tablets, FDA may be able to protect the public health by publishing a similar gradual phase-out of unapproved digoxin tablet distribution in the Final Rule on digoxin products.

While we believe that the record on this matter is complete, we would be pleased to meet with you to discuss our concerns.

Sincerely,

Gary L. Yingling

cc: Steven Galson, CDER
Jane Axelrad, CDER
Robert Temple, CDER
David Horowitz, CDER
Gary Buehler, OGD
Dockets Management Branch, Dockets No. 00N-1609, 00N-1610